AR201-13231

EASTMAN

Eastman Chemical Company
P.O. Box 511
Kingsport, Tennessee 37662

October 12, 2001

Ms. Christine Todd Whitman, Administrator
US EPA
PO Box 1473
Merrifield, VA 22116

Attn: Chemical Right-to-Know Program

RE: HPV Chemical Challenge Program, AR-201

Dear Ms Whitman:

On behalf of Eastman Chemical Company, I am pleased to submit the test plan and robust summaries for 2-pentanone (CAS No.: 107-87-9). Please note that in our March 12, 1999 commitment letter we called this chemical methyl propyl ketone. My company had agreed to sponsor this chemical and provide the Agency with the enclosed information in the year 2003. However, due to the substantial amount of data that had been previously generated to understand the potential hazards of this chemical, we were able to complete our summarization ahead of schedule.

Enclosed with this letter is a computer diskette containing the test plan and robust summaries in Adobe Acrobat (.pdf) format. The HPV registration number for Eastman Chemical is .

We understand this information will be posted on the internet for comments for a period of 120 days. Please forward comments to me at the above address.

Sincerely,

James A. Deyo D.V.M., Ph.D., D.A.B.T.
Technical Associate

AR201-13231A

HIGH PRODUCTION VOLUME (HPV) CHALLENGE PROGRAM

TEST PLAN
FOR
METHYL PROPYL KETONE
(CAS NO.: 107-87-9)

PREPARED BY:

EASTMAN CHEMICAL COMPANY

October 12, 2001

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OVERVIEW

The Eastman Chemical Company hereby submit for review and public comment the test plan for methyl propyl ketone (MPK; CAS NO.: 107-87-9) under the Environmental Protection Agency's (EPA) High Production Volume (HPV) Chemical Challenge Program. It is the intent of our company to use existing data in conjunction with EPA-acceptable predictive computer models, and values from reputable textbooks to adequately fulfill the Screening Information Data Set (SIDS) for the physicochemical, environmental fate, ecotoxicity test, and human health effects endpoints. We believe that these data are completely adequate to fulfill all the requirements of the HPV program without need for the conduct any new or additional tests.

Methyl propyl ketone is a colorless liquid capable of being manufactured to a high degree of purity. It has been reported to occur in many fruits, trees and shrubs, and is released naturally to the environment as a plant volatile, as a product of combustion, via photooxidation, and from microbial degradation of other chemicals. The FDA has approved its use in food under 21CFR 172.515. Nevertheless, this solvent finds its primary function as a solvent in various coating applications, in the electronics industry, as well as a solvent in industrial cleaning solutions. Industrial work place exposure levels for this chemical have been established by the ACGIH, which set a TLV-TWA of 200 ppm (705 mg/m^3).

TEST PLAN SUMMARY

CAS No. 107-87-9	Information	OECD Study	Other	Estimation	GLP	Acceptable	New Testing Required
STUDY	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N
PHYSICAL-CHEMICAL DATA							
Melting Point	Y	-	Y	-	N	Y	N
Boiling Point	Y	-	Y	-	N	Y	N
Vapor Pressure	Y	-	Y	-	N	Y	N
Partition Coefficient	Y	-	Y	-	N	Y	N
Water Solubility	Y	-	Y	-	N	Y	N
ENVIRONMENTAL FATE ENDPOINTS							
Photodegradation	Y	-	Y	-	N	Y	N
Stability in Water	Y[1]	-	-	Y	N	Y	N
Biodegradation	Y	Y	-	-	Y	Y	N
Transport between Environmental Compartments (Fugacity)	Y	-	-	Y	N	Y	N
ECOTOXICITY							
Acute Toxicity to Fish	Y	-	Y	-	N	Y	N
Acute Toxicity to Aquatic Invertebrates	Y	-	Y	-	N	Y	N
Toxicity to Aquatic Plants	Y	Y	-	-	Y	Y	N
TOXICOLOGICAL DATA							
Acute Toxicity	Y	-	Y	-	N	Y	N
Repeated Dose Toxicity	Y	-	Y	-	N	Y	N
Genetic Toxicity – Mutation	Y	-	Y	-	Y	Y	N
Genetic Toxicity – Chromosomal Aberrations	Y	Y	-	-	Y	Y	N
Developmental Toxicity	Y	Y	-	-	Y	Y	N
Toxicity to Reproduction	Y	Y	-	-	Y	Y	N

1. A technical discussion has been provided.

TEST PLAN DESCRIPTION FOR EACH SIDS ENDPOINT

A. Physicochemical

Melting point - A value for this endpoint was obtained from a reputable textbook referenced in Hazardous Substances Data Base (HSDB).

Boiling Point - A value for this endpoint was obtained from a reputable textbook referenced in HSDB.

Vapor Pressure - A value for this endpoint was obtained from a reputable textbook referenced in HSDB.

Partition Coefficient - A value for this endpoint was obtained from a reputable textbook referenced in HSDB.

Water Solubility - A value for this endpoint was obtained from a reputable textbook referenced in HSDB.

Conclusion: All end points haven been satisfied by the utilization of data obtained from various textbooks referenced within the HSDB. No new testing is required.

B. Environmental Fate

Photodegradation - A value for this endpoint was obtained from a manuscript referenced in HSDB.

Stability in Water - A technical discussion describing the stability of ketones in water was provided.

Biodegradation - This endpoint was satisfied through two studies. Both followed established guidelines and one was conducted under GLP assurances. (The other was conducted prior to the enactment of GLP.)

Fugacity - A value for this endpoint was obtained using the EQC Level III partitioning computer estimation model (1).

Conclusion: All endpoints have been satisfied using actual data or through the utilization of Agency-acceptable estimation models. In total they are of sufficient quality to conclude that no additional testing is needed.

C. Ecotoxicity Data

Acute Toxicity to Fish - This endpoint is filled by data from a well-conducted study completed prior to the enactment of GLP.

Acute Toxicity to Aquatic Invertebrates - This endpoint is filled by data from a well-conducted study completed prior to the enactment of GLP.

Toxicity to Aquatic Plants - This endpoint is filled by data from a study that followed an established OECD guideline (#201) and was conducted under GLP assurances.

Conclusion: All endpoints have been satisfied with data from well-conducted studies. The algal study followed OECD guidelines and GLP assurances, while the other two were conducted prior to the enactment of GLP. In total they are of sufficient quality to conclude that no additional testing is needed.

D. Toxicological Data

Acute Toxicity - This endpoint is filled by data from studies assessing toxicity following both oral and inhalation exposures. Oral studies evaluated both rats and mice while the inhalation study only utilized rats. None of the studies followed established protocols and they were conducted prior to the enactment of GLP. Nonetheless, sufficient information was available to ascertain the quality of these studies and to deem them "reliable with restrictions".

Repeat Dose Toxicity - This endpoint is filled by data from an oral drinking water study of 10 - 13 months duration and an inhalation study of 17.5 weeks duration. Neither study followed established protocols and were conducted prior to the enactment of GLP assurances. Nonetheless, sufficient information was available to ascertain the quality of these studies and to deem them "reliable with restrictions".

Genetic Toxicity
Mutation - This endpoint is filled with a single study in *Salmonella typhimurium* (strains TA 98, 100, 1535, 1537, and 1538) and *Escherichia coli* (strain WP2*uvr*A). This study followed an established guideline (EEC Annex V Guideline number B.14 and B.13) and was conducted under GLP assurances.

Aberration - This endpoint is filled with data from an *in vitro* study using Chinese hamster ovary (CHO) cells that followed an established OECD guideline (#473) and was conducted under GLP assurances.

Developmental
Toxicity - This endpoint is filled by data from an oral exposure study in rats that followed an established OECD guideline (#421) and was conducted under GLP assurances. This protocol evaluates both developmental and reproductive toxicity potential.

Reproductive
Toxicity - This endpoint is filled by data from an oral exposure study in rats that followed an established OECD guideline (#421) and was conducted under GLP assurances. This protocol evaluates both developmental and reproductive toxicity potential.

Conclusion: All endpoints have been satisfied with data from studies whose methods followed established guidelines, or utilized methods that were very similar and scientifically appropriate. Some studies were conducted under GLP assurances while some were conducted prior to its enactment. In total, they are of sufficient quality to conclude that no additional testing is needed.

SIDS DATA SUMMARY

Data assessing the various physicochemical properties (melting point, boiling point, vapor pressure, partition coefficient, and water solubility) for MPK were all obtained from textbooks referenced within the HSDB. These data indicate that MPK is a liquid at room temperature with a relatively high vapor pressure. It has a low estimated octanol to water partition coefficient and accordingly is quite soluble in water.

The assessment of the environmental fate endpoints (photodegradation, biodegradation, stability in water, and fugacity) was completed through the use of actual studies, acceptable estimation modeling programs, and a technical discussion. As a result of its relatively high solubility in water, fugacity estimations predict that MPK will distribute primarily to soil and water. A technical discussion has been provided that indicates this ketone is not anticipated to under go hydrolysis. Results from the two biodegradation studies indicate that, under the conditions of these assays, MPK is considered to be "readily biodegradable" in the environment. Nevertheless, due to its primary use in coatings applications, releases into the environment will primarily occur through evaporative emissions where degradation in the atmosphere is expected. The predicted half-life though for this route of elimination ranged from 26 – 79 hours.

The toxic potential of MPK to aquatic organisms and algae were determined through well-conducted studies. The results of these studies demonstrate that fish and Dapnia are not sensitive species, with NOEC's >1000 mg/l. Whereas, the 72-hour E_bC_{50} and E_rC_{50} values for algal effects indicate that MPK would not be classified as "harmful to aquatic organisms" according to the European Union's labeling directive and would be classified in a "moderate concern level" according to the U.S. EPA's assessment criteria. The potential for exposure to aqueous environments is unlikely due to its primary uses in coatings applications. Furthermore, it is noted as being readily biodegradable following exposure to wastewater microbes.

The potential to induce toxicity in mammalian species following acute oral and inhalation exposures is very low. The LD_{50} value noted in both rats and mice was between 1600-3200 mg/kg and an LC_{50} value of between 2000-4000 ppm following a 4-hour exposure. Repeat exposure data in rats following exposure durations of both 17.5 weeks (inhalation) and 10-13 months (through drinking water) indicate the material is tolerated quite well. The NOAEL in the 17.5- week study was 305 ppm (1,074 mg/m^3). This was the only concentration level examined in this study. In this study, there was no clinical signs or histological evidence of neurotoxicity exhibited at any exposure level. The only effect noted (seen in only one animal) in any of the tissues microscopically evaluated that was deemed to have been related to MPK exposure consisted of a very slight enlargement of hepatocytes. The NOAEL from the 10-month exposure study was 0.5% (250 mg/kg). In this study a slight decrease (maximum of 9% at Day 298) in body weight was seen at the highest dose (1.0%). There was no clinical or histological evidence of neurotoxicity exhibited by any of the treated animals in this study either. There was no effect on organ weights or lesions noted in any of the other many tissues microscopically evaluated. Results from mutagenicity and chromosomal aberration studies that utilized OECD guidelines and GLP assurances indicate this compound does not induce genotoxicity. Developmental and reproductive toxicity endpoints were assessed simultaneously through the conduct of a developmental/reproductive toxicity screening inhalation study in rats that followed OECD test guideline #421. Results from this study indicate MPK is not likely to induce either type of effect at dose levels up to 5 mg/L. Evidence of maternal effects were noted at 2.5 mg/L and higher, and consisted primarily of decreases in activity level.

In conclusion, an adequate assessment and summarization of all the Screening Information Data Set (SIDS) endpoints has been completed to satisfy the requirements of the HPV program without need for the conduct of any new or additional tests. This data set consists of results from studies conducted on MPK that either followed established protocols under GLP assurances or scientifically acceptable procedures to assess the various endpoints. Where appropriate, some endpoints have been fulfilled through the utilization of data from modeling programs accepted by the EPA. The summarized data indicate that this chemical, when used appropriately, should constitute a low risk to both workers and the general population.

EVALUATION OF DATA FOR QUALITY AND ACCEPTABILITY

The collected data were reviewed for quality and acceptability following the general US EPA guidance (2) and the systematic approach described by Klimisch *et al*. (3). These methods include consideration of the reliability, relevance and adequacy of the data in evaluating their usefulness for hazard assessment purposes. This scoring system was only applied to ecotoxicology and human health endpoint studies per EPA recommendation (4). The codification described by Klimisch specifies four categories of reliability for describing data adequacy. These are:

(1) Reliable without Restriction: Includes studies or data complying with Good Laboratory Practice (GLP) procedures, or with valid and/or internationally accepted testing guidelines, or in which the test parameters are documented and comparable to these guidelines.

(2) Reliable with Restrictions: Includes studies or data in which test parameters are documented but vary slightly from testing guidelines.

(3) Not Reliable: Includes studies or data in which there are interferences, or that use non-relevant organisms or exposure routes, or which were carried out using unacceptable methods, or where documentation is insufficient.

(4) Not Assignable: Includes studies or data in which insufficient detail is reported to assign a rating, e.g., listed in abstracts or secondary literature.

REFERENCES

1. EPIWIN, Version 1.2, Syracuse Research Corporation, Syracuse, New York.

2. USEPA (1998). 3.4 Guidance for Meeting the SIDS Requirements (The SIDS Guide). Guidance for the HPV Challenge Program. Dated 11/2/98.

3. Klimisch, H.-J., Andreae, M., and Tillmann, U. (1997). A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data. *Regul. Toxicol. Pharmacol.* 25:1-5.

4. USEPA. 1999. Determining the Adequacy of Existing Data. Guidance for the HPV Challenge Program. Draft dated 2/10/99.

I. General Information

CAS Number:	107-87-9
Name:	2-Pentanone
	Ethyl acetone
	Methyl propyl ketone
	Methyl-n-propyl ketone
	Methylpropyl ketone
	MPK

II. Physical-Chemical Data

A. Melting Point

Test Substance	
Test substance:	MPK
Remarks:	Purity unknown
Method	
Method:	Not Specified
GLP:	Unknown
Year:	Unknown
Remarks:	
Results	
Melting point value:	-78 °C
Kcmarks:	
Data Quality	
Remarks:	Data obtained from Hazardous Substances Data Bank Number: 158
References	Budavari, S. (Ed.). The Merck Index - Encyclopedia of Chemicals, Drugs and Biologicals. Whitehouse Station, NJ: Merck and Co., Inc 1996, 1043
Other	Last revision date: 1999092 1

B. Boiling Point

Test Substance	
Test substance:	MPK
Remarks:	Purity unknown
Method	
Method:	Not specified
GLP:	Unknown
Year:	Unknown
Remarks:	
Results	
Boiling point value:	101.7 ^{o}C
Pressure:	Not specified
Data Quality	
Remarks:	Data obtained from Hazardous Substances Data Bank Number: 158
References	Lewis, R.J., Sr. (Ed.). Hawley's Condensed Chemical Dictionary. 12th ed., New York, NY: VanNostrand Rheinhold Co., 1993, 779.
Other	Last revision date: 19990921

C. Vapor Pressure

Test Substance	
Test substance:	MPK
Remarks:	Purity unknown
Method	
Method:	Not specified
GLP:	Unknown
Year:	Unknown
Remarks:	
Results	
Vapor pressure value:	35.4 mmHg
Temperature:	25 ^{o}C
Remarks:	
Data Quality	
Remarks:	Data obtained from Hazardous Substances Data Bank Number: 158
References	Riddick, J.A., *et al*.; Techniques of Chemistry 4th ed., Volume II. Organic Solvents. New York, NY: John Wiley and Sons, 1985.
Other	Last revision date: 19990921

D. Partition Coefficient

Test Substance	
Test substance:	MPK
Remarks:	Purity unknown
Method	
Method:	Not specified
GLP:	Unknown
Year:	Unknown
Remarks:	
Results	
Log P_{OW}:	0.91
Temperature:	Unknown
Remarks:	
Data Quality	
Remarks:	Data obtained from Hazardous Substances Data Bank Number: 158
References	Hansch, C., Leo, A., and Hoekman. D.; Exploring QSAR – Hydrophobic, Electronic, and Steric Constants. Washington, DC: American Chemical Society; 1995, 14.
Other	Last revision date: 19990921

E. Water Solubility

Test Substance	
Test substance:	MPK
Remarks:	Purity unknown
Method	
Method:	Not specified
GLP:	Unknown
Year:	Unknown
Remarks:	
Results	
Value:	43 g/L
Temperature:	25 ^{o}C
Description:	Moderate (10-100 g/L)
Remarks:	
Data Quality	
Remarks:	Data obtained from Hazardous Substances Data Bank Number: 158
References	Yalkosky, S.H., Dannenfelser, R.M.; The AQUALSOL dATAbASE of Aqueous Solubility. 5th ed., Tucson, AZ: Univ. Az, College of Pharmacy, 1992.
Other	Last revision date: 19990921

III. Environmental Fate Endpoints

A. Photodegradation

Test Substance	
Test substance:	MPK
Remarks:	
Method	
Method:	Unknown
Test type:	Reaction with OH radicals
GLP:	No
Remarks:	
Results	
Conc. of substance:	Unknown
Temperature:	25 ^{o}C
Rate constant:	4.9 x 10^{-12} cm^3/molecule-sec
Half-life:	79-Hours (based on an average atmospheric hydroxyl radical concentration of 5 x 10^5 molecules/cm^3)
Remarks:	
Conclusions	Material is slowly degraded by atmospheric hydroxyl radicals.
Data Quality	
Remarks:	Data obtained from Hazardous Substances Data Bank Number: 158
References	Atkinson, R.; *J. Phys. Chem. Reference Data,* 1989.
Other	Last revision date: 19990921 The results from the EPIWIN modeling program yielded a half-life of 26.88 hours based on a similar rate constant of 4.77 x 10^{-12} cm^3/molecule-sec and an average atmospheric hydroxyl radical concentration of 1.5 x 10^6 molecules/cm^3.

B. Stability in Water

Reactivity of Selected Ketones With Water

This report has been prepared Dr. Paul Worsham of Eastman Chemical to document the known chemistry relevant to the stability of selected ketones in aqueous solution. The specific ketones addressed in this document are methyl propyl ketone (MPK; CAS# 107879), methyl isopropyl ketone (MIPK; CAS# 563804), methyl isoamyl ketone (MIAK; CAS# 110123), and methyl n-amyl ketone (MAK; CAS#110430).

Of particular concern in the evaluation of the stability of organic compounds in aqueous solution is the potential for hydrolysis. Hydrolysis is the reaction between water and an organic substrate resulting in the cleavage of existing chemical bonds and subsequent or simultaneous formation of new chemical bonds to form a different chemical compound. Typically, hydrolysis reactions involve incorporation of a water molecule into the structure of the reaction products. For organic substances that participate in hydrolysis reactions, various kinetic methods can be used to monitor the changes in concentration of reactants and determine the rate of transformation of the original substrate into reaction products. OECD Guideline 111 describes one such procedure for measuring the hydrolysis rate of water-soluble substrates as a function of pH. Substrates that exhibit high rates of hydrolysis are considered unstable in an aqueous environment.

Ketones as a class, and specifically the ketones identified above, do not participate in hydrolysis reactions. These ketones do not possess labile leaving groups that can be displaced by the nucleophilic attack of a water molecule, as is required in the mechanism of many hydrolysis reactions. Thus, it would not be meaningful to attempt to measure a hydrolysis rate using a protocol such as OECD Guideline 111.

Certain ketones may add water to form a hydrate under aqueous conditions, especially in the presence of mild acid; but, this addition is an equilibrium reaction that is reversible upon a change in water concentration, and the reaction ultimately leads to no permanent change in the structure of the ketone substrate.[1, 2]

A significant property of most ketones is that the hydrogen atoms on the carbons next to the carbonyl group are relatively acidic when compared to hydrogen atoms in typical hydrocarbons. Under strongly basic conditions these hydrogen atoms may be abstracted to form an enolate anion. This property allows ketones, especially methyl ketones such as the four ketones above, to participate in condensation reactions with other ketones and aldehydes. This reaction is called an aldol reaction and generates a higher molecular weight ketone having a hydroxyl group at the site of attack by the enolate anion. This type of condensation reaction is favored by high substrate concentrations and high pH (greater than 1 wt% NaOH). It is conceivable that some alkyl ketones, especially methyl ketones, could participate in aldol reactions in dilute aqueous solution at pH of 9 or higher. But, these reactions would be expected to be slow at ambient temperature, and the equilibrium for condensation of two ketones is unfavorable for aldol product formation[3]. Also, formation of the aldol product is reversible unless dehydration of the aldol occurs. Dehydration of an aldol intermediate in aqueous solution at ambient temperature also would be very slow.

Based on the properties of ketones described above one must conclude that MPK, MIPK, MIAK, and MAK are not subject to hydrolysis, but may participate in other transformations that convert the ketone to higher molecular weight compounds. These reactions would be expected to be very slow at mild temperatures and moderate pH. Therefore, it is my conclusion that MPK, MIPK, MIAK, and MAK should be considered stable in aqueous solution at temperatures and pH levels relevant to environmental and human exposure.

References:

(1) Bell and Clunie, *Trans. Faraday Soc.*, **48,** 439, (1952).
(2) Cohn and Urey, *J. Am. Chem. Soc.*, **60**, 679 (1938).
(3) March, J., ed. "Advanced Organic Chemistry", 3rd edition, p. 831, John Wiley & Sons, New York, 1985.

C. Biodegradation

Test Substance	
Test substance:	MPK
Remarks:	Purity unknown
Method	
Method:	Degradation; Method is similar to OECD: TG-301C: Modified MITI Test.
Test type:	Biochemical Oxygen Demand (BOD) and Chemical Oxygen Demand (COD)
GLP:	No (PreGLP)
Year:	1974
Remarks:	BOD was determined after 5 and 20 days.
Results	
Results:	BOD5 was 1.38 grams BOD/gram of test substance BOD20 was 1.8 grams BOD/gram of test substance COD was 1.8 grams oxygen/gram of test substance
Remarks:	
Conclusions	The test material is considered to be "Readily Biodegradable" based on a BOD5/COD ratio greater than 0.5. (1.38/1.8 = 0.77)
Data Quality	
Remarks:	While the detail from the referenced report is relatively scant, it is notable to point out that this study was conducted by a very reputable company with an established history of conducting this type of study.
References	Data are in report "Basic Toxicity of Methyl Propyl Ketone" Health, Safety and Human Factors Laboratory, Eastman Kodak Company, Rochester, NY; HS&HFL No. 74-305.
Other	

Test Substance	
Test substance:	MPK
Remarks:	Purity was 99.7%
Method	
Method:	OECD TG-301D
Test type:	Ready Biodegradability by the Closed Bottle Method
GLP:	Yes
Year:	2001
Contact time:	28-Days
Inoculum:	Activated sludge collected from Wareham, MA wastewater treatment plant
Remarks:	Benzoic acid at 10 mg/ml was used as a reference control. MPK was assessed at a nominal concentration of 2.5 mg/L. Test vessels of 300ml BOD bottles were prepared per treatment (reference, test substance and inoculum blank), two each for Day 0 and three per sampling interval (Days 7, 14, 21, and 28). After the bottles were filled they were closed and wrapped in tin foil.
Results	
Degradation % at test end:	70% (>60% by Day 14)
Classification:	Readily biodegradable
Remarks:	Benzoic acid reference was degraded 72%. The temperature of the environment ranged from 20-22 ^{o}C. Dissolved oxygen concentrations in the control blank ranged from 8.7 mg/L on Day 0 to 7.1 mg/L on Day 28. The protocol stated that oxygen depletion in the controls should not exceed 1.5 mg/L loss before Day 28; however, the loss was 1.6 mg/L. This protocol deviation was viewed as minor and does not affect the overall conclusion as it occurred well after Day 14 when the material had already met the ready biodegradable pass level of >60%.
Conclusions	Material is considered readily biodegradable under the conditions of this test.
Data Quality	
Remarks:	This was a well-documented study that followed established guidelines and was conducted under GLP assurances.
References	Methyl Propyl Ketone – Ready Biodegradability by the Closed Bottle Method; Springborn Laboratories, Inc Wareham, MA Study No. 1852.6174.
Other	

D. Transport between Environmental Compartments (Fugacity)

Test Substance	
Test substance:	MPK
Remarks:	
Method	
Test type:	Estimation
Model used:	Level III Fugacity Model; EPIWIN:EQC from Syracuse Research Corporation
Remarks:	
Results	
Model data and results:	Concentration (%)
Estimated distribution and media concentration (levels II/III):	Air 8.69 Water 50.5 Soil 40.7 Sediment 0.0651
Remarks:	Physical chemical values utilized in this model were default values obtained from the EPIWIN program.
Data Quality	
Remarks:	
References	Meylan, W. (1993). User's Guide for the Estimation Programs Interface (EPI), Version 1.2, Syracuse Research Corporation, Syracuse, New York 13210. The Level III model incorporated into EPIWIN is a Syracuse Research Corporation adaptation of the methodology described by Mackay *et al*. 1996; *Environ. Toxicol. Chem.* **15(9)**, 1618-1626 and *Environ. Toxicol. Chem.* **15(9)**, 1627-1637.
Other	

IV. Ecotoxicity

A. Acute Toxicity to Fish

Test Substance	
Test substance:	MPK
Remarks:	Purity unknown
Method	
Method:	Other
Test type:	Static
GLP:	No
Year:	1975
Species/strain:	Fathead minnow (*Pimephales promelas*)
Analytical monitoring:	Yes; Exposure solutions, temperature, pH, dissolved oxygen
Exposure period:	96-Hour
Remarks:	Water was filter-treated lake water with residual chlorine chemically removed. Twenty fish per dose level were used. Exposure solutions were submitted for temperature, dissolved oxygen, and pH concentration determinations at 0, 24, 48, 72, and 96 hrs. Observations for stress and mortality were conducted at 0, 0.5, 1, 6, 24, 48, 72, and 96 hours.
Results	
Nominal concentration:	100 and 1000 mg/L
Endpoint value:	LC_{50} >1000 mg/L; NOEC > 1000 mg/L
Biological observations:	No behavioral abnormalities were noted at any dose.
Statistical Methods:	NA; no effects were noted at any concentration
Remarks:	Exposure temperature ranged from 18-20 ^{o}C, pH was 7.6-8.0, and dissolved oxygen was 4.7-8.6 mg/L.
Conclusions	The LC_{50} value indicates that the test substance would not be classified according to the European Union's labeling directive and would correspond to a "low concern level" according to the U.S. EPA's assessment criteria.
Data Quality	
Reliability:	Reliable with restrictions
Remarks:	Study lacked some basic information as well as data indicating test material purity and analytical conformation of test concentrations.
References	An Acute Aquatic Effects Test with the Fathead Minnow; Environmental Sciences Section, Health and Environment Laboratories, at Eastman Kodak Company, Rochester, NY. HAEL No. 74-0305.
Other	

B. Acute Toxicity to Aquatic Invertebrates

Test Substance	
Test substance:	MPK
Remarks:	Purity unknown
Method	
Method:	Other
Test type:	Acute immobilization
GLP:	No
Year:	1975
Species/strain:	*Daphnia magna*
Analytical monitoring:	Yes; Exposure solutions, temperature, pH, dissolved oxygen
Exposure period:	96-Hour; static exposure
Remarks:	Water was filter-treated lake water with residual chlorine chemically removed. Twenty Daphnid per dose level were used. Exposure solutions were submitted for temperature, dissolved oxygen, and pH concentration determinations at 0, 24, 48, 72, and 96 hrs. Observations for stress and immobility were conducted at 0, ½, 1, 6, 24, 48, 72, and 96 hours.
Results	
Nominal concentration:	100 and 1000 mg/L
Endpoint value:	LC_{50} >1000 mg/L; NOEC > 1000 mg/L
Biological observations:	No behavioral abnormalities were noted at any dose.
Statistical Methods:	NA; no effects were noted at any concentration
Remarks:	Exposure temperature ranged from 18-20 ^{o}C, pH was 7.6-8.0, and dissolved oxygen was 4.7-8.6 mg/L.
Conclusions	The LC_{50} value indicates that the test substance would not be classified according to the European Union's labeling directive and would correspond to a "low concern level" according to the U.S. EPA's assessment criteria.
Data Quality	
Reliability:	Reliable with restrictions
Remarks:	Study lacked some basic information as well as data indicating test material purity and analytical conformation of test concentrations.
References	An Acute Aquatic Effects Test with the Daphnid (*Daphnia magna*); Environmental Sciences Section, Health and Environment Laboratories, at Eastman Kodak Company, Rochester, NY. HAEL No. 74-0305.
Other	

C. Toxicity to Aquatic Plants

Test Substance	
Test substance:	MPK
Remarks:	Purity was 99.8%
Method	
Method:	OECD: TG-201
Test type:	Growth inhibition of algae
GLP:	Yes
Year:	1998
Species/strain:	*Selenastrum capricornutum*
Endpoint basis:	Cell concentrations (biomass) and growth rate
Exposure period:	72-hours
Analytical procedures:	Temperature, light intensity, rpm, and test substance concentration were assessed at the 0, 24, 48, and 72 hours. The pH was assessed at time 0 and after 72 hours.
Remarks:	The concentration of algae at Day 0 was 10^4 cells/ml.
Results	
Nominal concentration:	0, 15.6, 31.2, 62.5, 125, 250 mg/L
Measured concentration:	0, 9.27, 17.81, 35.98, 73.77, 150.27 mg/L (geometric mean)
Endpoint value:	The estimated E_bC_{50} (0-72 hr) was 174.5 mg/L; the E_rC_{50} (0-72 hr) was 308.8 mg/L
NOEC, LOEC, or NOEL, LOEL:	The 72 hr NOEC was estimated to be 73.77 mg/L
Biological observations:	No deformed cells were noted
Was control response satisfactory:	Yes (a 110 fold increase in cell number was observed)
Statistical Methods:	Data were using descriptive statistics, plots, any applicable transformations, outlier tests, test for normality and heterogeneity of variance, regression techniques, the appropriate analysis of variance model (ANOVA) and Dunnett's test for comparison of treatment means to control.
Remarks:	A mean illumination of 743 foot-candles was maintained. The mean temperature was 24^oC and pH ranged from 7.48 to 7.72. Cultures were oscillated at 100 rpm. The significant loss (up to 71.1% over the course of the study) in test material was attributed to volatilization. No protocol deviations were noted.
Conclusions	The 72-hour E_bC_{50} and E_rC_{50} values indicate that, based on this study, the test substance would not be classified as "harmful to aquatic organisms" according to the European Union's labeling directive and would be classified in a "moderate concern level" according to the U.S. EPA's assessment criteria.
Data Quality	
Reliability:	Reliable without restrictions
Remarks:	This was a well-documented OECD-study conducted under GLP assurances
References	A Growth Inhibition Test with the Alga, *Selenastrum capricornum*; Environmental Sciences Section, Health and Environment Laboratories, Eastman Kodak Company, Rochester, NY; Study No. EN-512-901928-A; August 27, 1999
Other	

V. Toxicological Data

A. Acute Toxicity

Test Substance	
Test substance:	MPK
Remarks:	Purity unknown
Method	
Method:	Acute lethality; Other
Test type:	LD_{50} estimate
GLP:	No (Pre-GLP)
Year:	1974
Species/strain:	Rats
Sex:	Males
Animals/sex/dose:	2/dose
Vehicle:	None used
Route of exposure:	Oral gavage
Remarks:	Following an overnight fast, rats (2/dose) weighing 140-169 g were administered 200, 400, 800, 1600, or 3200 mg/kg test material. Following exposure animals were observed 14-days for clinical signs.
Results	
Value:	LD_{50} = 1600-3200 mg/kg
Deaths at each dose:	200 – 1600 mg/kg: No Mortalities 3200 mg/kg: Both rats died.
Remarks:	Immediately after dosing, the 200 mg/kg group showed slight weakness, while the 400 and 800 mg/kg dose groups were described as moderately to quite weak. The 1600 and 3200 mg/kg groups of animals were described as very weak and ataxic. Several hours after dosing, the 200, 400 and 800 mg/kg animals were slightly, moderately, or quite weak. The 1600 mg/kg animals had rough hair-coats and were very weak. Approximately 4.5 hours after dosing, one of the 3200 mg/kg animals died. The remaining rat was described as prostrate on the day of dosing and was found dead the following morning. All other animals survived the observation period and gained weight. No necropsies were conducted.
Conclusions	Material is considered slightly toxic (0.5 - 5 g/kg)
Data Quality	
Reliability:	Reliable with restrictions
Remarks:	Basic data are given
References	Study was conducted at Laboratory of Industrial Medicine, Eastman Kodak Company. Rochester, NY. Reference No. 74-305.
Other	

Test Substance	
Test substance:	MPK
Remarks:	Purity unknown
Method	
Method:	Acute lethality; Other
Test type:	LD_{50} estimate
GLP:	No (Pre-GLP)
Year:	1974
Species/strain:	Mice
Sex:	Males
Animals/sex/dose:	2/dose
Vehicle:	None used
Route of exposure:	Oral gavage
Remarks:	Following an overnight fast, rats (2/dose) weighing 25-27 g were administered 200, 400, 800, 1600, or 3200 mg/kg test material. Following exposure animals were observed 14-days for clinical signs.
Results	
Value:	LD_{50} = 1600-3200 mg/kg
Deaths at each dose:	200 - 800 mg/kg: No deaths occurred 1600 and 3200 mg/kg: One at each level
Remarks:	Immediately after dosing, animals in the 200, 400 and 800 mg/kg dose groups were slightly weak. The 1600 and 3200 mg/kg groups of animals were described as quite weak or prostrate. One of the 3200 mg/kg animals died approximately 1.3 hours after dosing. By several hours after dosing, one of two 1600 mg/kg animals was prostrate; all other surviving animals were slightly weak. The animal that had been prostrate remained very weak and did not eat on Day 1; this animal died on Day 6. All other animals survived a fourteen-day observation period and maintained or gained weight. No necropsies were conducted.
Conclusions	Material is considered slightly toxic (0.5 - 5 g/kg)
Data Quality	
Reliability:	Reliable with restrictions
Remarks:	Basic data are given
References	Study was conducted at Laboratory of Industrial Medicine, Eastman Kodak Company. Rochester, NY. Reference No. 74-305
Other	

Test Substance	
Test substance:	MPK
Remarks:	Purity unknown
Method	
Method:	Other
Test type:	Acute lethality estimate
GLP:	No (preGLP)
Year:	1962
Species/strain:	Rat/Charworth Wistar
Sex:	Unknown
Animals/sex/dose:	6
Vehicle:	None
Route of exposure:	Inhalation
Remarks:	Animals are exposed to vapor-air mixture generated by passing 2.5 L/min of dried air at room temperature through a fritted glass disc immersed at least one inch into test material contained in a gas-washing bottle. Inhalations are continued for time periods in a logarithmic series with a ratio of two extending from 15 minutes to 8 hours, until the inhalation period killing half the number of rats within 14 days is defined. Concentrations recorded are nominal.
Results	
Value:	LC_{50} 2000-4000 ppm (4-hours)
Deaths at each dose:	2000 ppm (0.5 hours): 0 of 6 died 2000 ppm (4 hours): 1 of 6 died 4000 ppm (4 hours): 6 of 6 died
Remarks:	
Conclusions	
Data Quality	
Reliability:	Reliable with restrictions
Remarks:	The manuscript in which this value was published lacked detail regarding the test material, methodologies, and description of clinical observations. Nevertheless, for the purpose of assessing acute lethality potential the data should be deemed reliable enough.
References	Smyth, H.F., Jr., Carpenter, C.P., Weil, C.S., Pozzani, U.C., and Striegel, J.A. Range-Finding Toxicity Data: List VI. *Industrial Hygiene Journal* March-April, 95-107, 1962.
Other	

B. Repeated Dose Toxicity

Test Substance	
Test substance:	MPK
Remarks:	Purity >97%
Method	
Method:	Other
Test type:	Repeated exposure
GLP:	No (PreGLP)
Year:	1978
Species/strain:	Rat/COBS CD (SD) BR
Route of exposure:	Oral; drinking water
Duration of test:	10-13 Months
Dose levels:	0.25% (10-months); 0.5% and 1.0% (13-months).
Sex:	Male (10/dose)
Exposure period:	Continuous in drinking water
Control group and treatment:	Yes, water absent test-article
Post-exposure observation period:	No
Remarks:	Animals (226-240 g) were housed singly in wire bottom cages and fed *ad libitum*. Drinking water containing test-compound was measured every other day to determine exposure. Animals were observed daily with body weight determinations and a neurological examination performed weekly. At termination animals were divided into two groups and processed for routine histological examination or underwent special fixation procedures for examination of nervous system tissues. The only organs weighed were the liver, kidney, and testes while microscopic examination was performed on 35 different organs or tissues. Clinical chemistries and hematological parameters were not assessed. In addition, only males were exposed.
Results	
NOEL:	0.5% (250 mg/kg)
Actual doses received:	Mean daily dose levels of 144, 250, and 454 mg/kg.
Toxic responses by dose:	Three animals died during study, one control, and one mid-dose and one from the high-dose level. The high-dose animal was euthanized due to a severe respiratory infection while the other treated animal died spontaneously from a massive renal hemorrhage. A slight decrease (maximum of 9% at Day 298) in body weight was seen at the 1.0% level. There was no clinical or histological evidence of neurotoxicity exhibited by any of the treated animals. There was no effect on organ weights or lesions noted in any of the other many tissues microscopically evaluated.
Statistical Methods:	Not described in report
Remarks:	
Conclusions	Animals appeared to tolerate exposure to MPK with minimal effects.

Data Quality	
Reliability:	Reliable with restrictions
Remarks:	This study was conducted before GLP assurances were enacted and lacked an assessment of other important parameters such as clinical chemistries and a second sex. Nevertheless, it was still a fairly well documented study and had an exposure period of between 10-13 months.
References	A Comparative Chronic Toxicity Study of Methyl n-Propyl Ketone, Methyl n-Butyl Ketone and Hexane. Health, Safety, and Human Factors Laboratory, at Eastman Kodak Company, Rochester, NY. August 14, 1978.
Other	

Test Substance	
Test substance:	MPK
Remarks:	Purity unknown
Method	
Method:	Other
Test type:	Repeated exposure to assess neurotoxic potential
GLP:	No (PreGLP)
Year:	1977
Species/strain:	Rat/Charles River CD
Route of exposure:	Inhalation
Duration of test:	17.5 weeks
Exposure levels:	305 ppm (1,074 mg/m^3)
Sex:	Male (5/dose)
Exposure period:	Two 16-hour periods and two 20-hour periods on 4 consecutive days
Control group and treatment:	Yes, air
Post-exposure observation period:	No
Remarks:	The main objective of this study was to assess the potential of MPK to induce neurotoxicity. Methyl n-butyl ketone was used as a positive control. In addition to special fixation of nervous tissue, 23 other tissues were harvested and processed in a routine manner for histological examination.
Results	
NOAEL:	305 ppm (1,074 mg/m^3)
Actual doses received:	Not reported
Toxic responses by dose:	There was no clinical signs or histological evidence of neurotoxicity exhibited by any of the MPK-treated animals. A very slight enlargement of hepatocytes was noted in one animal. This was the only effect noted that was deemed to have been possibly related to MPK exposure in any of the tissues microscopically evaluated.
Statistical Methods:	Not described in report
Remarks:	
Conclusions	Animals appeared to tolerate exposure to MPK with minimal effects.
Data Quality	
Reliability:	Reliable with restriction
Remarks:	The report from this study was deficient in both the detail of the methodology used and results. However, it does present data from a long-term inhalation exposure indicating this compound did not induce evidence of neurotoxicity.
References	Report TL-77-50; Health, Safety, and Human Factors Laboratory, at Eastman Kodak Company, Rochester, NY. February 21, 1977.
Other	

C. Genetic Toxicity - Mutation

Test Substance	
Test substance:	MPK
Remarks:	Purity was 95%
Method	
Method:	EEC Annex V Guideline number B.14 and B.13 (OECD:TG-471-like)
Test type:	*In vitro* mutagenicity
GLP:	Yes
Year:	1999
Species/strain:	*Salmonella typhimurium*/TA98, 100, 1535, 1537, and *Escherichia coli*/WP2*uvr*A(pKM101)
Metabolic activation:	Yes; Aroclor 1254-induced SD rat liver S9
Concentration tested:	Maximum concentration tested was 5000 ug/plate
Remarks:	Positive controls (2-aminoanthracene, 2-nitrofluorene, sodium azide, ICR-191, and 4-nitroquinoline-N-oxide) were run concurrently. Water was used as a vehicle control.
Results	
Result:	No positive responses were induced in any of the tester strains
Cytotoxic concentration:	>5000 ug/plate (no evidence of cytotoxicity was seen)
Precipitation concentration:	No precipitate was observed at the highest concentration tested.
Genotoxic effects	
With activation:	Negative
Without activation:	Negative
Statistical Methods:	Mean number of revertants and standard deviations were calculated. Various criteria were established to constitute a valid assay and a positive response was indicated by a 2-3 fold increase in mean revertant number dependent on the bacterial tester strain.
Remarks:	
Conclusions	Material was not genotoxic under conditions of this assay.
Data Quality	
Reliability:	Reliable without restrictions
Remarks:	This was a well-documented OECD guideline study conducted under GLP assurances.
References	Covance Laboratories Inc., Vienna, VA; Study No.: 20219-0-409R; March 8, 1999
Other	

D. Genetic Toxicity – Chromosomal Aberrations

Test Substance	
Test substance:	MPK
Remarks:	Purity was 95% (Lot No.:12-98)
Method	
Method:	OECD: TG-473
Test type:	*In vitro* mammalian chromosomal aberrations assay
GLP:	Yes
Year:	1999
Species/strain:	Chinese hamster ovary cells (CHO)
Concentrations tested:	Up to 900 ug/ml (this level exceeds the 10 mM max. recommended level)
Metabolic Activation:	Aroclor 1254-induced SD rat liver S9
Remarks:	The positive controls consisted of mitomycin-C and cyclophosphamide. Negative control was water.
Results	
Result:	No significant increases in cells with chromosomal aberrations, polyploidy, or endoreduplication were observed on analyzed cultures.
Cytotoxic concentration:	>1200 ug/ml (no evidence of cytotoxicity was seen)
Precipitation concentration:	No precipitate was observed at maximum concentration tested.
Genotoxic effects	
With activation:	Negative
Without activation:	Negative
Statistical Methods:	Statistical analysis employed a Cochran-Armitage test for linear trends and Fisher's Exact Test to compare the percentage of cells with aberrations.
Remarks:	
Conclusions	Material was not genotoxic under conditions of this assay.
Data Quality	
Reliability:	Reliable without restrictions
Remarks:	This was a well-documented OECD guideline study conducted under GLP assurances.
References	Covance Laboratories Inc., Vienna, VA; Study No.: 20216-0-437OECD; April 30, 1999
Other	

E. Developmental Toxicity

Test Substance	
Test substance:	MPK
Remarks:	Purity was >99%
Method	
Method:	OECD:TG-421
GLP:	Yes
Year:	1999
Species/strain:	Rats/Sprague-Dawley
Sex:	Male and Female (12/dose)
Route of exposure:	Inhalation, whole-body
Exposure levels:	0, 1, 2.5, or 5.0 mg/L
Actual exposure levels:	0, 1, 2.5, or 5.0 mg/L
Exposure period:	6 hrs/day
Frequency of treatment:	7 days/week
Control group and treatment:	Controls were treated and housed similarly
Duration of test:	Males were exposed for 51 days while females were exposed for 35 to 48 days. In addition to traditional female and fetal parameters and indices of toxicity, sperm, obtained from the epididymis on day of necropsy, was analyzed for motility. In addition testicular and epididymal sperm counts were conducted using an automated sperm analyzer.
Remarks:	
Results	
Maternal toxicity NOEL:	2.5 mg/L
Repro./Develop. toxicity NOEL:	>5.0 mg/L
Parental toxic responses:	There were no mortalities. A dose responsive reduction in activity was noted during the exposure period in the high-dose animals only. There was no effect on food consumption or body weight in either sex. There were no effects noted in any of the litter parameters due to MPK exposure (reproductive performance, gestation length, number of live/dead pups, implant total, prenatal loss, % survival, ratio of male/female pups, or pup weight). There were no effects noted in either sex on any of the selected organs that were weighed, or examined grossly or histologically. An increase in the mean absolute, but not body weight relative, epididymis weight was noted in the animals given 5 mg/L.
Fetal toxic responses dose:	There were no treatment-induced changes in pup clinical signs or abnormalities, or weight gains at any measured time-period.
Statistical Methods:	Mean values were calculated and assessed for homogeneity of variance using Bartlett's test followed by ANOVA and either Duncan's multiple range test or Dunnett's t-test. Non-homogeneous data were evaluated using Kruskal-Wallis H-test followed by Mann-Whitney U-test. Reproductive performance was evaluated in contingency table using Chi-square test.
Remarks:	
Conclusions	Test material did not induce any evidence of reproductive or developmental toxicity under the conditions of this assay.

Data Quality	
Reliability:	Reliable without restriction
Remarks:	This was a well-documented OECD guideline study conducted under GLP assurances.
References	Reproduction/Developmental Toxicity Screening Test in the Rat. Toxicological Sciences Laboratory, Health and Environment Laboratories, Eastman Kodak Company, Rochester, NY; Study Number HAEL 99-0201; October 6, 1999.
Other	

F. Toxicity to Reproduction

See robust summary E above which was a combined developmental/reproductive toxicity screening assessment.